REMARKS

Claims 1-20 are pending. Claims 1 and 2 and the specification have been amended. Support for these amendments can be found in the specification as follows:

1. In the specification, the inventors generically describe the formation of the claimed PEG-hGH conjugate: "In another preferred aspect of the invention, a **secondary amine linkage** is formed between the N-terminal primary α- or ε-amino group of hGH or agonist variant thereof and single or branched chain PEG aldehyde by **reductive alkylation** with a suitable reducing agent such as **$NACNBH_3$**, $NABH_3$, Pyridine Borane etc. **as described in Chamow *et al*[1].**, *Bioconjugate Chem*. 5: 133-140 (1994), US Pat No. 4,002,531[2], WO 90/05534[3], and **US Pat. No 5,824,784**[4]." (Paragraph 0054, page 20 of the specification of the application, as filed; emphasis added).

Chamow et al. illustrate this reaction in Figure 2. It shows the amine group (NH_2) of the amine-containing protein reacting with the aldehyde group (H(O=)C-)CH_2-OR) of the aldehyde to produce a conjugate in which the nitrogen atom of amine group is double-bonded to the carbon atom of the aldehyde group (-N=CH-) and then reduced with sodium cyanoborohydride ($NaCNBH_3$) to produce a conjugate having a secondary amine linkage (-NH-CH_2-):

[1] Reference no. 32 in IDS filed August 5, 2005.
[2] Reference no. 1 in IDS filed August 5, 2005.
[3] Reference no. 22 in IDS filed on August 5, 2005.
[4] Reference no. 10 in IDS filed August 5, 2005.

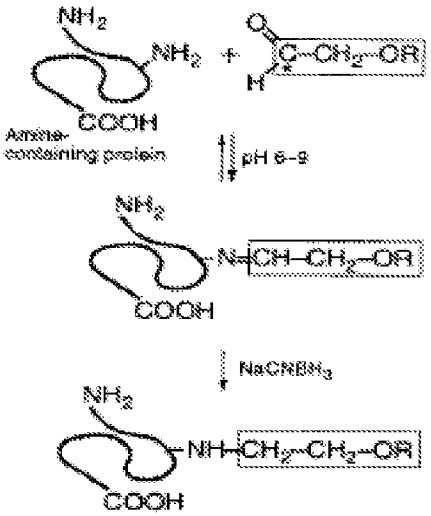
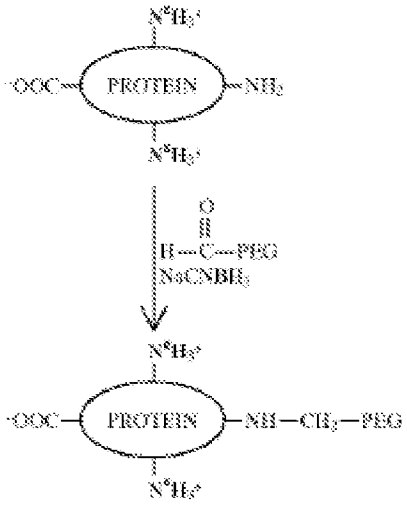


Figure 2. Conjugation of MePEG-CHO to protein amino groups via reductive alkylation. MePEG-CHO incubated with a protein at pH 6–9 results in reversible addition of MePEG to protein amino groups via Schiff's base formation. These linkages are converted to stable secondary amines by reduction with sodium cyanoborohydride. ε-Amino groups of lysine residues, as well as the α-amino group at the N-terminus, are targets for modification. The net charge of the modified protein does not change appreciably as a result of MePEGylation by this method, since primary amines are converted to secondary amines. Boxed region represents atoms derived from MePEG. R group and * as defined in Table 1.

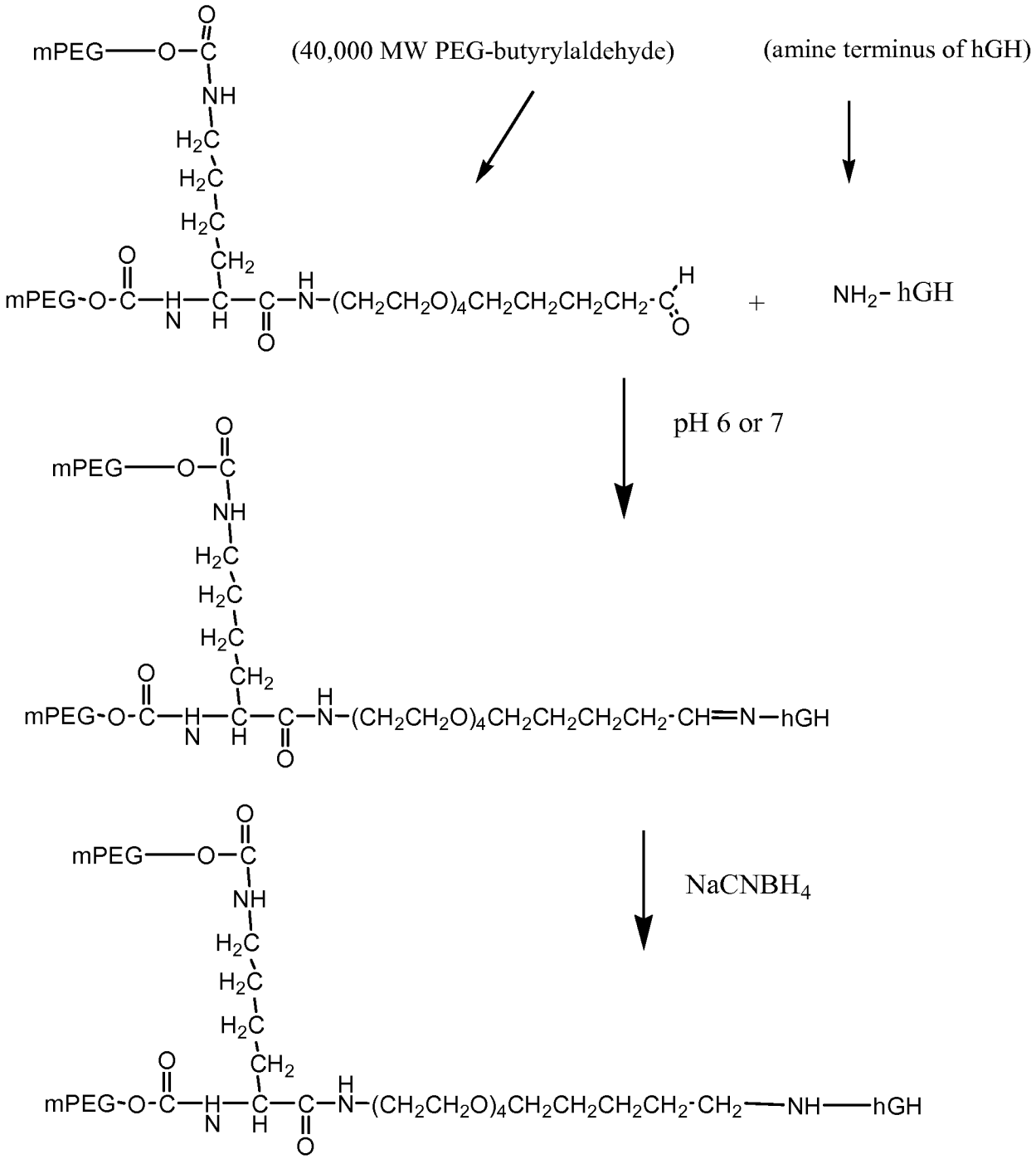
In U.S. Patent No. 5,824,784, Kinstler et al. similarly illustrate the reaction (see Column 8). Kinstler, et al., however, depict only the starting materials and the final product; that is, they do not show the intermediate containing the nitrogen-carbon double bond.



Notably, the product of Chamow et al.'s and Kinstler et al.'s reductive alkylation reactions does not contain a carbon-oxygen double bond. This bond is consumed in the reaction. Although they do not contain schematic illustrations of the reaction, US Pat No. 4,002,531 and WO 90/05534 describe the same types of starting materials, products and reactions. In each instance, the reaction product does not contain a carbon-oxygen double bond at the point of attachment.

2. Example 1 describes the preparation of a PEG-hGH conjugate using a methoxy-branched PEG butyrylaldehyde and hGH. Consistent with the description of the chemistry in the specification (Paragraph 0054, page 20 of the specification of the application, as filed), the conjugate is formed by **reductive alkylation** between the N-terminal α-amino group of hGH and the methoxy-branched PEG butyraldehyde using **$NACNBH_3$** as the reducing agent. The reaction described in Example 1 is illustrated in the following reaction.

Reaction Scheme For Example 1



As illustrated by Chamow et al. and Kinstler et al. and as described in applicant's specification, the conjugate product contains a secondary amine linkage (-NH-CH_2-) at the point of attachment: ["In another preferred aspect of the invention, **a secondary amine linkage** is formed between the N-terminal primary α- or ε-amino group of hGH or

agonist variant thereof and single or branched chain PEG ***aldehyde*** **by reductive alkylation** with a suitable reducing agent such as **$NACNBH_3$**, $NABH_3$, Pyridine Borane etc. as described in Chamow et al., Bioconjugate Chem. 5: 133-140 (1994), US Pat No. 4,002,531, WO 90/05534, and US Pat. No 5,824,784." (Paragraph 0054 (page 21, lines 19-27) of the specification; emphasis added)]

3. The formula for the methoxy-branched PEG butyrylaldehyde employed in Example 1 is depicted in the example. It corresponds to the branched conjugate appearing in paragraph 0043 (page 16 of the application, as filed) and in claim 2, with one exception: the branched conjugate appearing on page 16 and in claim 2 are terminated by -NHR wherein R is hGH, and -NH is the N-terminal α-amino group of hGH.

4. Formula I is a generic formula for the branched conjugate of paragraph 0043 (page 16 of the application, as-filed).

5. Examples 2 and 3 describe the preparation of a PEG-hGH conjugate using a methoxy-linear PEG butyrylaldehyde instead of a methoxy-branched butyrylaldehyde; otherwise, the conditions were as described in Example 1. Consistent with the description of the chemistry in paragraph 0054 (page 21, lines 19-27) of the specification, the conjugates of Examples 2 and 3 are formed by reductive alkylation between the N-terminal α-amino group of hGH and the methoxy-branched PEG butyraldehyde or methoxy-linear PEG butyraldehyde using $NACNBH_3$ as the reducing agent.

6. The formulae for the methoxy-linear PEG butyrylaldehyde employed in Examples 2 and 3 corresponds to the linear conjugate appearing in paragraph 0043 (page 16 of the application, as-filed) and in claim 2, with one exception: the linear conjugate appearing in paragraph 0043 (page 16 of the application, as filed) and in claim 2 are terminated by -NHR wherein R is hGH, and -NH is the N-terminal α-amino group of hGH.

7. Formula II is a generic formula for the linear conjugate of paragraph 0043 (page 16 of the application, as filed).

8. Consistent with the description of the chemistry in paragraph 0054 (page 20 of the application, as-filed) of the specification, the conjugates of Examples 1, 2 and 3 are formed by **reductive alkylation** between the N-terminal α-amino group of hGH and the methoxy-branched PEG butyraldehyde or methoxy-linear PEG butyraldehyde using **$NACNBH_3$** as the reducing agent.

From the foregoing, it is apparent (i) Formulae I and II are generic to structures depicted in paragraph 0043 (page 16 of the application, as-filed), (ii) the structures of paragraph 0043 (page 16 of the application, as-filed) and claim 2 were intended to specifically cover the conjugate produced by the reactions described in Examples 1, 2 and 3, and (iii) Formulae I and II were intended to generically cover the conjugate produced by the reactions described in Examples 1, 2 and 3 and paragraph 0054 of the specification (page 20 of the application, as-filed). Furthermore, it is apparent that through error, Formulae I and II contain an **amide linkage** when they should have shown a **secondary amine** linkage, which a person of ordinary skill would have understood from (i) the description of the chemistry used in the examples (reductive alkylation with $NACNBH_3$), (ii) the description appearing in paragraph 0054 of the specification (page 20 of the application, as-filed), and (iii) the references identified in paragraph 0054 of the specification (page 20 of the application, as-filed).

Restriction Requirement

Reconsideration of the restriction requirement is respectfully requested. According to 35 U.S.C. §121, a restriction is proper only if there are at least two independent and distinct inventions. Furthermore, "[i]f the search and examination of an entire application can be made **without serious burden**, the Examiner must examine it on the merits, even though it includes claims to independent or distinct inventions."[5]

In this case, restriction is not proper. The claims of Group I and Group II each have a common element; each of the Group II claims recites the use of a human growth hormone conjugate specified by one of the Group I claims. Any search of the prior art and examination involving Group I claims therefore, will substantially co-extend with the search and examination of Group II claims and vice versa. Thus, the Group II claims may be searched and examined along with the Group I claims without undue burden in accordance with MPEP §803.

Subject to the foregoing traverse, Applicants elect the claims of Group I (claims 1-9 and 15) drawn to the composition. The species elected for purposes of examination is the species of claim 2 (Claim 1 wherein m=3, n=4, R=human growth hormone); claims 1-9 and 15 each read upon the elected species.

Applicants reserve the right to file divisional applications directed to the non-elected subject matter.

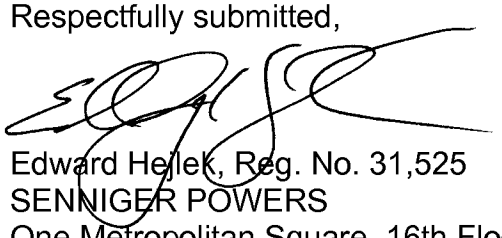
[5] MPEP § 803 (emphasis added).

CONCLUSION

In light of the foregoing, Applicants respectfully request entry of the claim amendments, and solicit an allowance of the claims.

The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

Respectfully submitted,



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